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The Parabolic Dependence of Drug Action upon Lipophilic Character as Revealed by a Study of Hypnotics

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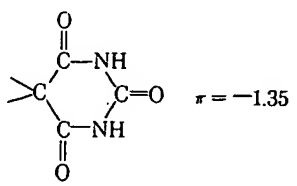
Evidence is presented that the hypnotic activity of groups of barbiturates depend almost entirely on their relative lipophilic character as defined by their octanol–water partition coefficients. Ideal lipophilic character is defined for each set by the constant log P_0. This constant for the barbiturates is about 2. It is shown that many other sets of hypnotics structurally unrelated to the barbiturates also have log P_0 values near 2. It is also shown that the rate of metabolism of barbiturates is linearly related to their partition coefficients. Certain guidelines are suggested for the design of new CNS depressants.

It has long been known that the relative activity of drugs in a series of congeners is highly dependent on their lipophilic character. It has also been appreciated tacitly that linear relations between relative activity and lipophilic character do not hold indefinitely as the latter continues to increase. However, with the exception of the efforts by Ferguson[3] to rationalize this fall of activity which inevitably occurs when derivatives of a parent drug are made sufficiently lipophilic, most workers have ignored the problem or assumed that it was too unruly to deal with in precise terms. Our working hypothesis has assumed[4-6] that such fall-off in activity was the result of the decrease in mobility of drug movement through biological material when one departed in either direction from ideal lipophilic character. That is, assuming all other factors except lipophilic character to be constant for a given set of congeners producing a specific biological reaction, there should exist for the set an ideal balance between hydrophobic and hydrophilic interactions of the drug so that those members possessing this ideal balance would find the sites of action through a random-walk process in the minimum time. Or, to put it another way, the concentrations of these drugs reaching the reaction sites in the test interval, Δt, would be maximum for the set. We have chosen 1-octanol and water to represent the two extremes of the biophase. The partition coefficient, P, is a measure of the preference of drugs for hydrophilic or lipophilic phase. Equation 1 formulates our model. In eq 1, C is the molar concentration of applied drug producing a standard biological response and k, k', and k'' are constants obtained *via* the method of least squares. Setting the derivative d log $(1/C)$/d log P equal to zero and solving the resulting equation for log P yields what we have termed log P_0, the ideal lipophilic character for the set of congeners under the specific test conditions. We have postulated[6-8] that this should be a particularly useful constant in drug research. For example, once log P_0 or π_0 is found for a group of congeners, one has a meaningful point from which to start the design of a completely new set of congeners to cause the same response. The purpose of this paper is to examine a variety of different hypnotics by fitting the experimental results to eq 1 and to compare the log P_0 values for the different sets. Hypnotics were chosen because of the large amount of experimental data in the literature. Even so, we were surprised by the paucity of examples in which sufficient spread in activity was investigated and quantitatively reported, so that log P_0 could be calculated with any degree of certainty.

$$\log \frac{1}{C} = -k(\log P)^2 + k' \log P + k'' \qquad (1)$$

Method

In a preliminary report on barbiturates,[7] we correlated substituent effects for a single series using π values for substituents and log P for barbituric acid as our base of reference. In a subsequent study[9] we used



$\pi = -1.35$

(1) John Simon Guggenheim Fellow.
(2) Smith Kline and French Research Associate.
(3) J. Ferguson, *Proc. Roy. Soc.* (London), **B127**, 387 (1939).
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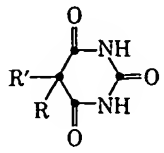
TABLE I

OBSERVED AND CALCULATED CONCENTRATIONS OF BARBITURATES CAUSING HYPNOSIS



No.	R	R′	Log P	Log (1/C) Obsd[a]	Log (1/C) Calcd[b]	|Δ Log (1/C)|
1	Methyl	1-Methyl-1-propenyl	0.65	2.64	2.767	0.13
2	Ethyl	1-Methyl-1-propenyl	1.15	3.15	3.163	0.01
3	Propyl	1-Methyl-1-propenyl	1.65	3.29	3.340	0.05
4	Allyl	1-Methyl-1-propenyl	1.35	3.39	3.260	0.13
5	Butyl	1-Methyl-1-propenyl	2.15	3.36	3.298	0.06
6	Methyl	1-Methylvinyl	0.15	2.12	2.153	0.03
7	Ethyl	1-Methylvinyl	0.65	2.91	2.767	0.14
8	Propyl	1-Methylvinyl	1.15	3.04	3.163	0.12
9	Allyl	1-Methylvinyl	0.85	3.06	2.952	0.11
10	Butyl	1-Methylvinyl	1.65	3.33	3.340	0.01
11	Isobutyl	1-Methylvinyl	1.45	3.27	3.296	0.03
12	Amyl	1-Methylvinyl	2.15	3.32	3.298	0.02
13	Isoamyl	1-Methylvinyl	1.95	3.26	3.341	0.08
				Obsd[c]	Calcd[d]	
14	Ethyl	Ethyl	0.65[r]	3.09	3.012	0.08
15	Propyl	Propyl	1.65	3.55	3.656	0.11
16	Propyl	Isopropyl	1.45	3.63	3.628	0.00
17	Butyl	Butyl	2.65	2.84	3.040	0.20
18	Ethyl	Isopropyl	0.95	3.30	3.338	0.04
19	Ethyl	Isobutyl	1.45	3.63	3.628	0.00
20	Ethyl	Butyl	1.65	3.72	3.656	0.06
21	Ethyl	Isoamyl	1.95	3.75	3.604	0.15
22	Propyl	Isoamyl	2.45	3.48	3.264	0.22
23	Ethyl	Phenyl	1.42[r]	3.46	3.620	0.16
24	Ethyl	*sec*-Butyl	1.45	3.63	3.628	0.00
				Obsd[e]	Calcd[f]	
25	Ethyl	1-Methylbutyl	1.95	4.05	3.976	0.07
26	Ethyl	1-Ethylbutyl	1.95	3.95	3.976	0.03
27	Methyl	1-Methylbutyl	1.45	3.63	3.686	0.06
28	Propyl	1-Methylbutyl	2.45	3.90	4.001	0.10
29	Propyl	1-Ethylpropyl	2.45	3.78	4.001	0.22
30	Allyl	1-Methylbutyl	2.15	4.20	4.018	0.18
31	Allyl	1-Ethylpropyl	2.15	4.08	4.018	0.06
32	Butyl	1-Methylbutyl	2.95	3.86	3.763	0.10
33	Butyl	1-Ethylpropyl	2.95	3.75	3.763	0.01
				Obsd[g]	Calcd[h]	
34	Ethyl	2-Methylallyl	1.15	3.23	3.252	0.02
35	Propyl	2-Methylallyl	1.65	3.27	3.369	0.10
36	Isopropyl	2-Methylallyl	1.45	3.35	3.333	0.02
37	Butyl	2-Methylallyl	2.15	3.38	3.401	0.02
38	Isobutyl	2-Methylallyl	1.95	3.36	3.399	0.04
39	*sec*-Butyl	2-Methylallyl	1.95	3.42	3.399	0.02
40	Amyl	2-Methylallyl	2.65	3.26	3.346	0.09
41	*sec*-Amyl	2-Methylallyl	2.45	3.62	3.379	0.24
42	2-Methylbutyl	2-Methylallyl	2.45	3.34	3.379	0.04
43	3-Methylbutyl	2-Methylallyl	2.45	3.36	3.379	0.02
44	1-Ethylpropyl	2-Methylallyl	2.45	3.50	3.379	0.12
45	Hexyl	2-Methylallyl	3.15	3.18	3.205	0.03
46	2-Ethylbutyl	2-Methylallyl	2.95	3.25	3.272	0.02
47	Cyclopentyl	2-Methylallyl	2.29	3.40	3.394	0.01
48	Allyl	2-Methylallyl	1.35	3.44	3.309	0.13
49	2-Methylallyl	2-Methylallyl	1.65	3.37	3.369	0.00
50	Phenyl	2-Methylallyl	1.92	3.24	3.397	0.16
				Obsd[i]	Calcd[i]	
51	Allyl	Allyl	1.05	3.54	3.392	0.15
52	Ethyl	Allyl	0.85	3.28	3.238	0.04
53	Propyl	Allyl	1.35	3.47	3.540	0.07
54	Isopropyl	Allyl	1.15	3.60	3.452	0.15
55	Butyl	Allyl	1.85	3.47	3.570	0.10
56	Isobutyl	Allyl	1.65	3.63	3.591	0.04
57	*sec*-Butyl	Allyl	1.65	3.78	3.591	0.19

[a] Fro
ref 17.
[b] Calcu
Satd me
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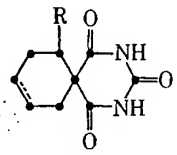
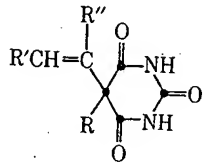
TABLE I (*Continued*)

No.	R	R′	Log *P*	Log (1/*C*) Obsd[i]	Log (1/*C*) Calcd[j]	|Δ Log (1/*C*)|
58	Isoamyl	Allyl	2.15	3.45	3.457	0.01
59	Ethyl	Ethyl	0.65[r]	2.91	3.041	0.13
60	Butyl	Ethyl	1.65	3.53	3.591	0.06
61	Isopropyl	Ethyl	0.95	3.34	3.320	0.02
62	Isoamyl	Ethyl	1.95	3.59	3.543	0.05
63	Butyl	Isopropyl	1.95	3.49	3.543	0.05
64	Butyl	Butyl	2.65	3.08	3.051	0.03
65	Phenyl	Ethyl	1.42[r]	3.32	3.561	0.24
				Obsd[k]	Calcd[l]	
66	Propyl	1-Propenyl	1.35	3.12	3.191	0.07
67	Isopropyl	1-Propenyl	1.15	3.28	2.976	0.30
68	Butyl	1-Propenyl	1.85	3.31	3.485	0.18
69	Ethyl	1-Butenyl	1.35	3.37	3.191	0.18
70	Propyl	1-Butenyl	1.85	3.31	3.485	0.18
71	Isopropyl	1-Butenyl	1.65	3.57	3.409	0.16
72	Butyl	1-Butenyl	2.35	3.56	3.435	0.12
73	Ethyl	2-Methyl-1-propenyl	1.15	2.56	2.976	0.42
74	Ethyl	1-Pentenyl	1.85	3.45	3.485	0.04
75	Isopropyl	1-Pentenyl	2.15	3.50	3.497	0.00
76	Ethyl	3-Methyl-1-butenyl	1.65	3.51	3.409	0.10
77	Propyl	3-Methyl-1-butenyl	2.15	3.32	3.497	0.18
78	Isopropyl	3-Methyl-1-butenyl	1.95	3.68	3.503	0.18



No.	R	Ring	Log *P*	Log (1/*C*) Obsd[m]	Log (1/*C*) Calcd[n]	|Δ Log (1/*C*)|
79	Methyl	Unsatd[o]	0.75	2.69	2.690	0.00
80	Ethyl	Unsatd[o]	1.25	2.96	3.090	0.13
81	Propyl	Unsatd[o]	1.75	3.27	3.372	0.10
82	Isopropyl	Unsatd[o]	1.55	3.28	3.273	0.01
83	3,4,5-Trimethyl	Unsatd[o]	1.55	3.13	3.273	0.14
84	Methyl	Satd	1.05	3.06	2.944	0.12
85	Ethyl	Satd	1.55	3.33	3.273	0.06
86	Propyl	Satd	2.05	3.65	3.485	0.16
87	Isopropyl	Satd	1.85	3.55	3.414	0.14
88	Isobutyl	Satd	2.35	3.45	3.555	0.11

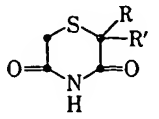


No.	R	R′	R″	Log *P*	Log (1/*C*) Obsd[p]	Log (1/*C*) Calcd[q]	|Δ Log (1/*C*)|
89	Methyl	Ethyl	Methyl	1.15	3.21	3.125	0.09
90	Ethyl	Ethyl	Methyl	1.65	3.65	3.439	0.21
91	Propyl	Ethyl	Methyl	2.15	3.56	3.632	0.07
92	Isopropyl	Ethyl	Methyl	1.95	3.98	3.569	0.41
93	Methyl	Methyl	Ethyl	1.15	3.06	3.12	0.07
94	Ethyl	Methyl	Ethyl	1.65	3.40	3.43	0.04
95	Propyl	Methyl	Ethyl	2.15	3.42	3.63	0.21
96	Isopropyl	Methyl	Ethyl	1.95	3.72	3.569	0.15
97	Methyl	Propyl	Methyl	1.65	3.27	3.439	0.17
98	Ethyl	Propyl	Methyl	2.15	3.64	3.632	0.01
99	Methyl	Isopropyl	Methyl	1.45	3.20	3.328	0.13
100	Methyl	Butyl	Methyl	2.15	3.38	3.632	0.25
101	Ethyl	Butyl	Methyl	2.65	3.75	3.706	0.04
102	Ethyl	Ethyl	Propyl	2.65	3.75	3.706	0.04

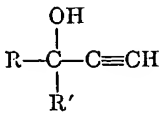
[a] From ref 14. [b] Calculated using eq 2. [c] From ref 15. [d] Calculated using eq 3. [e] From ref 16. [f] Calculated using eq 4. [g] From ref 17. [h] Calculated using eq 5. [i] From ref 18. [j] Calculated using eq 6. [k] From ref 19. [l] Calculated using eq 7. [m] From ref 20. [n] Calculated using eq 8. [o] Unsatd indicates that the spirane ring contains a double bond in the position indicated by the dotted line. Satd means the ring was saturated. [p] From ref 21. [q] Calculated using eq 9. [r] These values for log *P* were experimentally determined; all others were calculated. See ref 9.

TABLE II

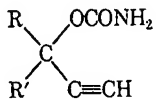
OBSERVED AND CALCULATED CONCENTRATIONS OF NONBARBITURATES CAUSING HYPNOSIS



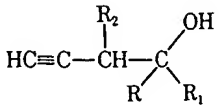
No.	R	R′	Log P	Log (1/C) Obsd[a]	Log (1/C) Calcd[b]	|Δ Log (1/C)|
103	Methyl	Methyl	0.50	2.40	2.429	0.03
104	Ethyl	Ethyl	1.50[c]	2.97	2.854	0.12
105	Propyl	Propyl	2.50	2.78	2.842	0.06
106	Butyl	Butyl	3.50	2.40	2.390	0.01
107	Ethyl	Butyl	2.50	3.02	2.842	0.18
108	Ethyl	Phenyl	2.27	2.67	2.883	0.21



No.	R	R′	Log P	Log (1/C) Obsd[c]	Log (1/C) Calcd[d]	|Δ Log (1/C)|
109	Methyl	Ethyl	1.18	2.59	2.660	0.07
110	Ethyl	Ethyl	1.68	2.98	2.904	0.08
111	Methyl	Cyclopropyl	1.39	2.79	2.805	0.02
112	Methyl	Vinyl	0.88	2.41	2.349	0.06
113	Ethyl	Vinyl	1.38	2.79	2.799	0.01
114	Isopropyl	Vinyl	1.68	2.92	2.904	0.02
115	Butyl	Vinyl	2.38	2.65	2.670	0.02
116	Methyl	Isopropenyl	1.18	2.62	2.660	0.04
117	Methyl	Ethyl	1.18	2.59[e]	2.665[f]	0.08
118	Methyl	Vinyl	0.88	2.41	2.340	0.07
119	Ethyl	Vinyl	1.38	2.79	2.831	0.04
120	Isopropyl	Vinyl	1.68	2.92	3.003	0.08
121	Methyl	Chlorovinyl	1.50	2.94	2.911	0.03
122	Ethyl	Chlorovinyl	2.00	3.20	3.086	0.11
123	Propyl	Chlorovinyl	2.50	2.90	3.006	0.11
124	Isopropyl	Chlorovinyl	2.30	3.17	3.068	0.10



No.	R	R′	Log P	Log (1/C) Obsd[g]	Log (1/C) Calcd[h]	|Δ Log (1/C)|
125	Methyl	Ethyl	0.89	2.86	2.997	0.14
126	Methyl	Vinyl	0.59	2.74	2.667	0.07
127	Ethyl	Vinyl	1.09[c]	3.11	3.150	0.04
128	Isopropyl	Vinyl	1.39	3.31	3.278	0.03
129	Methyl	Chlorovinyl	1.21	3.28	3.215	0.07
130	Ethyl	Chlorovinyl	1.71[c]	3.32	3.280	0.04
131	Propyl	Chlorovinyl	2.21	3.00	3.008	0.01
132	Isopropyl	Chlorovinyl	2.01	3.13	3.157	0.03



No.	R	R_1	R_2	Log P	Log (1/C) Obsd[i]	Log (1/C) Calcd[j]	|Δ Log (1/C)|
133	Methyl	Methyl	H	0.85	2.15	2.216	0.07
134	Methyl	Ethyl	H	1.35	2.50	2.473	0.03
135	Methyl	Ethyl	Methyl	1.65	2.50	2.570	0.07
136	Methyl	Vinyl	H	1.05	2.44	2.332	0.11
137	Ethyl	Ethyl	H	1.85	2.70	2.612	0.08
138	Ethyl	Ethyl	Methyl	2.15	2.67	2.643	0.03
139	Methyl	Isopropyl	H	1.65	2.70	2.570	0.13
140	Methyl	Isopropyl	Methyl	1.95	2.54	2.629	0.09
141	Methyl	Cyclopropyl	H	1.56	2.39	2.545	0.16
142	Methyl	*t*-Butyl	H	2.03	2.30[k]	2.635	0.34
143	Methyl	2-Methylpropenyl	H	1.85	2.24[k]	2.612	0.37

TABLE II (*Continued*)

Tertiary Alcohols

No.	Compd	Log *P*	Log (1/*C*) Obsd[l]	Log (1/*C*) Calcd[m]	|Δ Log (1/*C*)|
144	Cyclopropylmethylethylcarbinol	1.60	2.82	2.804	0.02
145	Cyclopropylmethylethynylcarbinol	1.39	2.68	2.731	0.05
146	1-Ethylcyclopentanol	1.53	2.77	2.784	0.01
147	1-Ethynylcyclopentanol	1.32	2.74	2.698	0.04
148	1-Ethylcyclohexanol	1.94	2.89	2.846	0.04
149	1-Ethynylcyclohexanol	1.73[r]	2.84	2.831	0.01
150	1-Ethynyl-4-methylcyclohexanol	2.23	2.89	2.806	0.08
151	Ethynylethylmethylcarbinol	1.18	2.51	2.620	0.11
152	Ethynylmethylvinylcarbinol	0.88	2.68	2.400	0.28
153	Cyclopropylmethylallylcarbinol	1.80	2.80	2.840	0.04
154	Cyclopropylmethylbenzylcarbinol	2.69	2.55	2.599	0.05
155	Cyclopropylmethylphenylcarbinol	2.30	2.25[k]	2.787	0.54
156	Ethyldimethylcarbinol	0.89[r]	2.20	2.408	0.21

$(CH_3)_2C(SR)CONH_2$

No.	R	Log *P*	Log (1/*C*) Obsd[n]	Log (1/*C*) Calcd[o]	|Δ Log (1/*C*)|
157	Methyl	0.32	2.28	2.270	0.01
158	Propyl	1.32	2.91	2.753	0.16
159	Isopropyl	1.12	2.68	2.707	0.03
160	Allyl	1.02	2.61	2.674	0.06
161	Crotyl	1.52	2.70	2.775	0.08
162	2-Propynyl	0.80	2.58	2.580	0.00

N,N′-Diacylureas

No.	N	N′	Log *P*	Log (1/*C*) Obsd[p]	Log (1/*C*) Calcd[q]	|Δ Log (1/*C*)|
163	Acetyl	Propionyl	−0.10	1.84	1.831	0.01
164	Propionyl	Propionyl	0.40	2.06	2.104	0.04
165	Acetyl	Butyryl	0.40	2.16	2.104	0.06
166	Butyryl	Propionyl	0.90	2.23	2.288	0.06
167	Acetyl	Valeryl	0.90	2.27	2.288	0.02
168	Butyryl	Butyryl	1.40[r]	2.40	2.383	0.02
169	Propionyl	Valeryl	1.40	2.35	2.383	0.03
170	Acetyl	Hexanoyl	1.40	2.46	2.383	0.08
171	Butyryl	Valeryl	1.90	2.38	2.390	0.01
172	Hexanoyl	Propionyl	1.90	2.25	2.390	0.14
173	Acetyl	Heptanoyl	1.90	2.55	2.390	0.16
174	Valeryl	Valeryl	2.40	2.32	2.308	0.01
175	Butyryl	Hexanoyl	2.40	2.28	2.308	0.03
176	Heptanoyl	Propionyl	2.40	1.96[k]	2.311	0.35

[a] From ref 22. [b] Calculated using eq 10. [c] From ref 23. [d] Calculated using eq 11. [e] From ref 24. [f] Calculated using eq 12. [g] From eq 24. [h] Calculated using eq 13. [i] From ref 25. [j] Calculated using eq 14. [k] These points were not used in determining the constants. [l] From ref 26. [m] Calculated using eq 15. [n] From ref 27. [o] Calculated using eq 16. [p] From ref 28. [q] Calculated using eq 17. [r] See footnote *r*, Table I.

calculated from log *P* for diethyl barbiturate. In this tudy we have again used −1.35 for the 5,5-substituted barbiturate function and, taking advantage of the additive-constitutive character[8-13] of π and log *P*, calculated the values in Table I as before.[9] The phenyl group in phenobarbital and other such derivatives has a π value lower than one would expect from benzene (log 2.13). It has been our experience[11b] that whenever aromatic rings are present with polar functions in a side chain, log *P* is lower than one would expect from the simple additivity principle. Apparently dipolar interaction with the π electrons of the aromatic system results in a more compact molecule having greater than expected water solubility. Thus π for the phenyl group in phenylethylbarbituric acid is calculated to be 1.77 [1.42 − (−1.35 + 1.00) = 1.77]. This value for the phenyl group has been used in calculating log *P* for compound **108** in Table II.

The biological activities of the various hypnotics were assayed by different techniques. The original work[14-21] should be consulted for details.

Table II contains the relative activities of a variety of hypnotics[22-28] whose activities appear to be the same

(10) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).

(11) (a) J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, **8**, 150 (1965); (b) C. Hansch and S. M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967).

(12) D. J. Currie, C. E. Lough, R. F. Silver, and H. L. Holmes, *Can. J. Chem.*, **44**, 1035 (1966).

(13) P. Bracha and R. D. O'Brien, *J. Econ. Entomol.*, **59**, 1255 (1966).

(14) A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, **61**, 353 (1939).

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(16) D. L. Tabern and E. H. Volwiler, *ibid.*, **56**, 1139 (1934).

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(18) E. H. Volwiler, *ibid.*, **47**, 2236 (1925).

(19) A. C. Cope, W. H. Hartung, E. M. Hancock, and F. S. Crossley, *ibid.*, **62**, 1199 (1940).

(20) A. C. Cope, P. Kovacic, and M. Burg, *ibid.*, **71**, 3658 (1949).

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(22) G. S. Skinner and J. B. Bicking, *ibid.*, **76**, 2776 (1954).

(23) S. Y. P'an, L. Markarian, W. M. McLamore, and A. Bavley, *J. Pharmacol. Exptl. Therap.*, **109**, 268 (1953).

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(26) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **77**, 4874 (1955).

(27) H. Lehr, L. O. Randall, and M. W. Goldberg, *J. Med. Chem.*, **6**, 351 (1963).

(28) R. W. Stoughton, *J. Org. Chem.*, **2** 514 (1938).

type as that of the barbiturates. These particular sets were chosen because log P values were available for a representative member or relatively easily measured. The excellent review of Doran[29] was of great help in locating sets of barbiturates. Equally useful for the nonbarbiturate hypnotics was the review by Wheeler.[30] Table II summarizes the data on the nonbarbiturates.

The log P values for the thiamorpholinediones (**103–108**) were based on the experimental value of 1.50 for the diethyl derivative. For each methylene group, 0.5 was added or subtracted to obtain log P for the other derivatives.

Log P for the acetylenic alcohols, **109–116**, was calculated using for $C(OH)C{\equiv}CH$ $\pi = -0.32$. This was obtained by subtracting five-cyclic CH_2 units[9] ($5 \times 0.41 = 2.05$) from the experimental value of 1.73 for 1-ethynylcyclohexanol. The value of 0.7 was used for the vinyl group and 1.21 for the cyclopropyl moiety.[9] We have found that an isoalkyl function is 0.2 unit less than a normal chain and that vinyl is 0.3 unit less than ethyl. Thus isopropenyl is calculated by subtracting these figures from 1.50: $1.50 - 0.3 - 0.2 = 1.00 =$ log P for isopropenyl. The value for chlorine attached to a vinyl group was found by subtracting log P for **127** from **130**. This value of 0.62 is, as one would expect, rather close to 0.71 for chlorine in benzene. For aliphatic Cl, $\pi = 0.39$.

For compounds **133–143**, π for $HC{\equiv}C-$ (0.48) was added to log P for t-butyl alcohol (0.37) to obtain log $P = 0.85$ for the basic structure, $HC{\equiv}CCH_2C(OH)(CH_3)_2$. Where $R_2 = CH_3$, 0.3 was added to the basic structure. For **141**, the difference between a methyl and a cyclopropyl group was added to the basic structure. The same procedure was used for **150** and **151** (π for t-butyl = 1.68).

For the tertiary alcohols **144–156** the value of π for $>COH$ was found by subtracting 2.00 from log P of 0.89 for t-amyl alcohol. This value of -1.11 was used except in those molecules having an acetylenic group attached to the carbinol function. In these examples we have used -0.32 for the unit $>C(OH)C{\equiv}CH$. For example, for **144** log P = methyl + ethyl + cyclopropyl + $>COH = 0.50 + 1.00 + 1.21 - 1.11 = 1.60$. The substituents on **154** were summed as usual except that in this example 0.6 unit was subtracted for the interaction between the OH and the aromatic ring.[11b] Compound **155** was calculated as **154** except that 0.43 unit was subtracted for OH interaction with the ring.[11b]

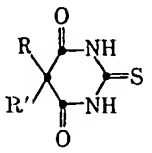
Log P values for **157–162** were based on the value of 1.82 found for $(CH_3)_2C(SC_4H_9)CONH_2$.

Log P values for molecules **163–176** were based on the dibutyryl derivative (log P = 1.40). To check the additivity principle in this series we also measured log P for the diacetyl derivative (−0.68). The difference between these two compounds is 2.08. The value of four CH_2 units is 2.00; hence, additivity holds very well.

In Table III we have summarized the relative activities[31–33] for three sets of thiobarbiturates. The log P values for these compounds were calculated from the base value of 3.23 for 5-allyl-5-(1-methylbutyl)thiobarbituric acid, 2.19 for 5-ethyl-5-(2-methyl-2-propenyl)thiobarbituric acid, and 2.98 for isopentylethylthiobarbituric acid as follows. From 3.23 was sub-

TABLE III

OBSERVED AND CALCULATED CONCENTRATIONS OF THIOBARBITURATES CAUSING HYPNOSIS



No.	R	R′	Log P	Log (1/C) Obsd[a]	Log (1/C) Calcd[b]	$\lvert\Delta$ Log (1/C)$\rvert$
177	Methyl	Isopropenyl	1.20	2.55	2.573	0.02
178	Ethyl	Isopropenyl	1.70	3.03	2.980	0.05
179	Propyl	Isopropenyl	2.20	3.19	3.225	0.04
180	Allyl	Isopropenyl	1.90	3.11	3.098	0.01
181	Butyl	Isopropenyl	2.70	3.29	3.305	0.02
182	Amyl	Isopropenyl	3.20	3.24	3.223	0.02
183	Isoamyl	Isopropenyl	3.00	3.27	3.275	0.01
				Obsd[c]	Calcd[d]	
184	Isoamyl	Ethyl	3.00	4.06	4.186	0.13
185	1-Methylbutyl	Ethyl	3.00	4.28	4.186	0.09
186	Hexyl	Ethyl	3.70	4.09	4.072	0.02
187	Ethyl	Ethyl	1.70	3.37	3.400	0.03
188	Allyl	Isopropyl	2.20	3.93	3.856	0.07
189	*sec*-Butyl	Allyl	2.70	4.28	4.120	0.16
190	Butyl	Ethyl	2.70	3.94	4.120	0.18
				Obsd[e]	Calcd[f]	
191	Ethyl	Ethyl	1.70	3.40	3.436	0.04
192	Isopropyl	Ethyl	2.00	3.83	3.740	0.09
193	Butyl	Ethyl	2.70	4.03	4.223	0.19
194	*sec*-Butyl	Ethyl	2.50	4.16	4.118	0.04
195	2-Methylallyl	Ethyl	2.20	3.85	3.911	0.06
196	Isoamyl	Ethyl	3.00	3.89[g]	4.331	0.44
197	1-Methylbutyl	Ethyl	3.00	4.36	4.332	0.03
198	2-Ethylbutyl	Ethyl	3.50	4.39	4.383	0.01
199	Allyl	Allyl	2.10	3.85	3.829	0.02
200	2-Methylallyl	Allyl	2.40	4.05	4.055	0.01
201	*sec*-Butyl	Allyl	2.70	4.36	4.223	0.14

[a] From ref 31. [b] Calculated using eq 18. [c] From ref 32. [d] Calculated using eq 19. [e] From ref 33. [f] Calculated using eq 20. [g] This point was not used in the regression analysis.

TABLE IV

PER CENT BARBITURATE EXCRETED UNCHANGED

R	R′	Log P	Log % Obsd[a]	Log % Calcd[b]	$\lvert\Delta$ Log$\rvert$. %
Allyl	Isopropyl	1.15	1.27	1.274	0.00
Ethyl	Ethyl	0.65[c]	1.89	1.892	0.00
Allyl	Allyl	1.05	1.46	1.397	0.06
Ethyl	Phenyl	1.42[c]	1.26	0.941	0.32
Methyl	Phenyl	0.92	1.40	1.558	0.16
Ethyl	*sec*-Butyl	1.45	0.60	0.903	0.30
2-Bromoallyl[d]	*sec*-Butyl	2.45	−0.52	−0.332	0.19
Ethyl	1-Cyclohexenyl	1.95	0.65	0.286	0.36
Ethyl	*sec*-Amyl	1.95	0.18	0.286	0.11
2-Bromoallyl[d]	Isopropyl	1.95	0.30	0.286	0.01

[a] This value represents the log of the average per cent excreted, unchanged barbiturate. From ref 38. [b] Calculated using eq 21. [c] See footnote *r*, Table I. [d] The value of π for Br attached to an olefinic bond was taken as 0.80 in calculating log P.

(29) F. F. Blicke and R. H. Cox, "Medicinal Chemistry," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1959, p 1.

(30) E. E. Campaigne and W. H. Hartung, "Medicinal Chemistry," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1963, p 1.

(31) A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, **61**, 96 (1939).

(32) O. M. Gruhzit, A. W. Dox, L. W. Rowe, and M. C. Dodd, *J. Pharmacol. Exptl. Therap.*, **60**, 125 (1937).

(33) D. L. Tabern and E. H. Volwiler, *J. Am. Chem. Soc.*, **57**, 1961 (1935).

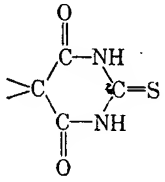
TABLE V

METABOLISM OF BARBITURATES

R	R'	Log P	Log % metabolized Obsd[a]	Calcd[b]	|Δ Log|, %
		In Liver			
Allyl	1-Methylbutyl	2.15	1.45	1.41	0.04
Ethyl	Isoamyl	1.95	1.26	1.31	0.05
Ethyl	1-Methylbutyl	1.95	1.31	1.31	0.00
Allyl	Isopropyl	1.15	0.91	0.90	0.01
		In Mice			
Allyl	1-Methylbutyl	2.15	1.95	1.96[c]	0.01
Ethyl	Phenyl	1.42	1.52	1.50	0.02
Ethyl	Ethyl	0.65	1.00	1.01	0.01

[a] From ref 39. [b] Calculated using eq 22. [c] Calculated using eq 23.

tracted 1.20 + 2.30 for the two substituents in the 5 position to give −0.27 for



In the second of the above cases 2.19 − 1.00 − 1.50 = −0.31 and in the third 2.98 − 1.00 − 2.30 = −0.32. The average of the three values is 0.30 for the thiobarbiturate function with two substituents in the 5 position. To this base was added π for the alkyl groups to get the log P values in Table III.

The critical feature of this report is the comparison of log P_0 values for various sets of hypnotics. Since there is often a good deal of scatter in the data from which our calculations are made, it is very important to know, in so far as possible, what kind of confidence one can place in any particular log P_0 value. For this reason we deem it essential, when possible, to report confidence intervals on this constant. We have used the method of Roy and Potthoff[34] in building this calculation into our computer program.

In the regression relationship

$$Y_i = \log \frac{1}{C_i} = \beta_0 + \beta_1\pi_i + \beta_2\pi_i^2 + \beta_3\sigma_i + \epsilon_i \quad (2)$$

(log P may be substituted for π) where ϵ_i is the error term, the estimator $\hat{\beta}$ of the vector

$$\begin{vmatrix}\beta_0\\ \beta_1\\ \beta_2\\ \beta_3\end{vmatrix}$$

is $\hat{\beta} = (X'X)^{-1}X'Y$ where X is the matrix

$$\begin{vmatrix}1 & \pi_1 & \pi_1^2 & \sigma_1\\ 1 & \pi_2 & \pi_2^2 & \sigma_2\\ 1 & \pi_3 & \pi_3^2 & \sigma_3\\ \vdots & \vdots & \vdots & \vdots\\ 1 & \pi_N & \pi_N^2 & \sigma_N\end{vmatrix}$$

and

$$Y = \begin{vmatrix}Y_1\\ Y_2\\ Y_3\\ \vdots\\ Y_N\end{vmatrix}$$

(34) S. N. Roy and R. F. Potthoff, *Ann. Math. Statist.*, **29**, 829 (1958).

An estimator of the variance of ϵ_i is $s^2 = (Y'Y - \hat{\beta}'X'Y)/(N - 4)$. The variance–covariance matrix for the $\hat{\beta}$ vector is $\sigma^2(X'X)^{-1}$ where σ^2 (σ must not be confused with σ_i of eq 2 which is the Hammett constant) can be estimated by s^2. Denote the elements of $(X'X)^{-1}$ by

$$\begin{vmatrix}\nu_{00} & \nu_{01} & \nu_{02} & \nu_{03}\\ \nu_{10} & \nu_{11} & \nu_{12} & \nu_{13}\\ \nu_{20} & \nu_{21} & \nu_{22} & \nu_{23}\\ \nu_{30} & \nu_{31} & \nu_{32} & \nu_{33}\end{vmatrix}$$

A $(1 - \alpha)$ 100% confidence interval for $-\beta_1/2\beta_2 = \pi_0$ or log P_0 is given in eq 3. In eq 3, $t = t_{N-4}^{1-\alpha/2}$

$$-(\hat{\beta}_1\hat{\beta}_2 - t^2s^2\nu_{12})/[2(\hat{\beta}_2^2 - t^2s^2\nu_{22})] \pm [(\hat{\beta}_1\hat{\beta}_2 - t^2s^2\nu_{12})^2 - (\hat{\beta}_1^2 - t^2s^2\nu_{11})(\hat{\beta}_2^2 - t^2s^2\nu_{22})]^{1/2}/[2(\hat{\beta}_2^2 - t^2s^2\nu_{22})] \quad (3)$$

is that point in Students' distribution with $N - 4$ degrees of freedom which is preceded with probability $1 - \alpha/2$.

Two situations can arise which will lead to meaningless confidence intervals. The denominator of the limits in eq 3 might be negative. If this occurs we can conclude that a confidence interval for β_2 covers zero, and hence the confidence interval for $\pi_0(\log P_0) = -\beta_1/2\beta_2$ includes both $+\infty$ and $-\infty$. The other problem can occur if that quantity in the numerator is imaginary. This arises when the proper confidence interval for π_0 is $(-\infty, \infty)$. In either case the confidence interval gives no useful information for the experimenter concerning the true value of π_0 or log P_0 and hence is meaningless. Therefore we have had to list some values of log P_0 without confidence intervals. The fact that in general the confidence interval does not center at $-\hat{\beta}_1/2\hat{\beta}_2$ should be noted in eq 3.

Results

Fitting the data in Table I to eq 1 yields eq 1a–h, the coefficients and constants of which are given in Table VI. In these equations, C represents the moles of drug per kilogram of test animal producing "hypnosis," r is the correlation coefficient, and s the standard deviation. The ± numbers represent the 90% confidence intervals on the intercept and the range with log P_0 is the 90% confidence interval on this constant. Unfortunately, the results contained in eq 1a–h were derived from data obtained in a variety of laboratories during the quarter century 1923–1949. Not only was hypnosis defined in different ways such as ED and MED_{50}, but some workers used rabbits, some mice, and some rats. Four of the papers were by Cope and coworkers.[14,19–21] However, even here there is a great difference between the testing technique reported in the first paper in 1939 and the last paper in 1949. Considering the differences in the testing techniques and the great variation in the type of groups in the 5 position, it is not surprising that the coefficients differ from equation to equation. Even so, the general agreement is not bad. Of greatest interest are the log P_0 values. The mean value for the five sets for which it was possible to calculate confidence intervals is 1.9. In the Method section we have discussed the reason why confidence intervals cannot be given for sets 1f–h.

Omitting eq 1f we find a mean value for the intercepts of approximately 2. Comparison of the multiple correlation coefficients, r, indicates a considerable range

TABLE VI

$$\text{Log}\,\frac{1}{C} = -k(\log P)^2 + k' \log P + k''$$

Compd	Test	Coeff $(\log P)^2$	Coeff $\log P$	Constant	r	s	Log P_0	Eq
1-13	AD_{50} (mice)	−0.438	1.579	1.926 ± 0.20	0.969	0.098	1.80 (1.65–2.08)	1a
14–24	MED (rabbits)	−0.630	2.092	1.918 ± 0.58	0.896	0.140	1.66 (1.54–1.78)	1b
25–33	MED (rabbits)	−0.529	2.377	1.351 ± 1.94	0.744	0.139	2.25 (1.95–2.49)	1c
34–50	MAD (rats)	−0.173	0.719	2.653 ± 0.58	0.531	0.099	2.08 (1.67–2.38)	1d
51–65	MED (rats)	−0.545	1.804	2.098 ± 0.43	0.855	0.124	1.65 (1.55–1.77)	1e
66–78	AD_{50} (mice)	−0.690	2.797	0.672 ± 2.36	0.702	0.219	2.03	1f
79–88	ND_{50} (mice)	−0.236	1.273	1.867 ± 0.78	0.915	0.132	2.69	1g
89–102	AD_{50} (mice)	−0.240	1.300	1.948 ± 1.42	0.737	0.914	2.71	1h

in the goodness of fit. Part of the poor correlation, notably that of eq 1d, is due to the small amount of initial variance in the data. That is, this variance is not much greater than the variation due to experimental error. This problem occurs because some of the workers appeared to have reported on only the most active members of a series.

In deriving eq 1a–h we have not attempted to include terms for electronic and steric effects of substituents since previous work[9] has indicated that these effects are so small that they can be omitted for the type of barbiturates under consideration. The reasonably good correlations contained in this paper also support this assumption. The generally good agreement obtained in the eight different investigations comprising 102 examples is strong support for our hypothesis[6] that, other factors remaining constant, biological response as defined by log $(1/C)$ is parabolically dependent on log P. The fact that all but two of the values for log P in Table I were calculated rather than determined experimentally is further evidence for the utility of the additive-constitutive nature of log P.

It is indeed a satisfaction that such a diverse set of data can be treated mathematically, and one cannot escape the feeling that if all of the tests had been run on one type of animal in one laboratory, the agreement would have been much better.

We have been investigating the hypothesis that sets of congeners acting by the same mechanism on the same receptor sites should have the same log P_0 values, *other factors being constant*. Since the barbiturates act strongly on the central nervous system (CNS), we now have in hand data to support this hypothesis in an independent way. Soloway[35] and his co-workers have measured the rate at which members of a set of benzeneboronic acids were localized in mouse brain tissue. Fitting his data to eq 1 allows us to calculate log P_0 for this series. The value of 2.32 (2.05–3.18) agrees well with that we have found for the barbiturates. In the case of the boronic acids we know we are talking about the rate at which this set of congeners finds the brain since it was determined by chemical analysis. In the case of the barbiturates, we are inferring that biological response reflects the concentration of hypnotic in the CNS. The above findings prompted us to calculate log P_0 for other sets of hypnotics. Equations 1i–p in Table VII result from least-squares fits of the data in Table II to eq 1. One would not expect eq 1i–p to have the same intercepts, since different sets of congeners as well as different tests are involved. However, it is most interesting and not altogether unexpected that they have about the same mean value for log P_0 found for the barbiturates (1.8). In arriving at this figure we have omitted log P_0 values from sets 1m and 1p for which confidence intervals could not be found. All things considered, the agreement between the two groups of equations is striking, especially with the wide variety of functional groups used to obtain eq 1i–p. These results are in line with our earlier finding[9] (as well as those of many others) about the nonspecific inhibitory action of organic compounds on a variety of oxidative processes. It would appear as though almost any organic compound having log $P \sim 2$ which is not rapidly metabolized or eliminated from the body would have some hypnotic properties.

The data on thiobarbiturates from Table VIII yield eq 1q–s. Results in eq 1q–s from three different groups of investigators give fair agreement on the ideal lipophilic character for the three different sets of drugs. The mean log P_0 is 3.1. The thiobarbiturates quite definitely do not fit into the same pattern shown by the other barbiturates or the other hypnotics. Their maximum activity is attained when their partition coefficient is about 10 times that of the barbiturates. This strongly implies a different over-all mechanism of action. That the thiobarbiturates have quite different biological action from the oxybarbiturates has been pointed out by Aldridge and Parker.[36]

We have emphasized[6] the fact that for nonequilibrium conditions, as one makes a particular functional unit more lipophilic by the addition of inert apolar atoms, one expects to see a departure from the linear, Meyer–Overton relationship. We feel that simple, nonspecific binding by proteins and lipids is sufficient to cause this effect. In addition to such binding, the metabolism of lipophilic drugs also contributes to this effect. As Brodie as well as McMahon have pointed out and as we have shown in quantitative terms,[37] liver mitochondria seem to attack C–H bonds rather nonspecifically. The rate-limiting factor seems to be the relative lipophilic character of the organic compound. This also holds for barbiturates. From the data (Table IV) assembled by Maynert and Van Dyke[38] on the per cent unchanged barbiturate eliminated, we have derived eq 4. The negative coefficient with log P in eq

$$\log \%\ \text{unchanged barbiturate} = -1.235 \log P + 2.695 \qquad (4)$$

$n = 10$, $r = 0.957$, $s = 0.224$

(35) A. H. Soloway, B. Whitman, and J. R. Messer, *J. Pharmacol. Exptl. Therap.*, 129, 310 (1960).

(36) W. N. Aldridge and V. H. Parker, *Biochem. J.*, 76, 47 (1960).

(37) C. Hansch, A. R. Steward, and J. Iwasa, *J. Med. Chem.*, 8, 868 (1965).

(38) E. W. Maynert and H. B. Van Dyke, *Pharmacol. Rev.*, 1, 217 (1949).

TABLE VII

$$\text{Log } \frac{1}{C} = -k(\log P)^2 + k' \log P + k''$$

Compd	Test	Coeff $(\log P)^2$	Coeff $\log P$	Constant	r	s	Log P_0	Eq
103–108	HD_{50} (mice)	−0.219	0.864	2.501 ± 0.67	0.858	0.178	1.97 (1.29–2.74)	1i
109–116	HD_{50} (mice)	−0.686	2.451	0.724 ± 0.50	0.965	0.058	1.79 (1.71–1.88)	1j
117–124	HD_{50} (mice)	−0.510	2.134	0.857 ± 0.84	0.944	0.105	2.09 (1.91–2.68)	1k
125–132	HD_{50} (mice)	−0.675	2.099	1.663 ± 0.45	0.947	0.082	1.56 (1.47–1.68)	1l
133–143	MHD (rabbits)	−0.231	1.020	1.516 ± 1.08	0.826	0.114	2.21	1m
144–156	ED_{50} (guinea pigs)	−0.414	1.589	1.322 ± 0.64	0.805	0.130	1.92 (1.75–2.24)	1n
157–162	HD_{50} (mice)	−0.314	0.999	1.983 ± 0.54	0.913	0.108	1.59	1o
163–176	MED (mice)	−0.177	0.599	1.893 ± 0.10	0.918	0.079	1.69 (1.50–2.05)	1p

TABLE VIII

$$\text{Log } \frac{1}{C} = -k(\log P)^2 + k' \log P + k''$$

Compd	Test	Coeff $(\log P)^2$	Coeff $\log P$	Constant	r	s	Log P_0	Eq
177–183	AD_{50} (mice)	−0.327	1.763	0.928 ± 0.35	0.994	0.035	2.70 (2.59–2.85)	1q
184–190	MAD (rats)	−0.834	2.409	0.414 ± 2.04	0.919	0.150	3.13 (2.84–4.60)	1r
191–201	MED (rabbits)	−0.326	2.221	0.602 ± 1.37	0.958	0.102	3.41 (3.06–4.84)	1s

4 indicates that the more lipophilic the barbiturate, the less recovered unchanged. Over the range of log P values considered, this effect is linearly dependent on log P. Hence the chances of lipophilic barbiturates reaching the active sites in time to register in a given test are lowered by their destruction. Since this process depends so heavily[37] on log P, one obtains good correlations with eq 1 despite metabolic loss. So long as loss (metabolic or through macromolecular binding) is dependent only on log P and not on highly specific structural or electronic features, eq 1 holds. The good correlations of eq 1a–s of course support this point. Equation 4 is only an approximation since it comes from investigations which were not highly quantitative. However, it is supported by the metabolic studies of Dorfman and Goldbaum.[39]

From the data in Table V we have formulated eq 5 and 6. Equation 5 comes from the *in vitro*, liver me-

	n	r	s	
log % metabolized = 0.511 log P + 0.313	4	0.987	0.063	(5)
log % metabolized = 0.634 log P + 0.599	3	0.999	0.026	(6)

tabolism studies with barbiturates and eq 6 from *in vivo* metabolic work with mice. The data from which these two equations were derived are also only approximate. However, the results are in qualitative agreement with eq 4 in that metabolic destruction is linearly dependent on log P.

Discussion

Our results do provide further evidence for the practical value of the concept of log P_0 in drug design. It is worth considering some of the factors which determine its value. Disregarding for the moment metabolism or elimination, we have postulated that, steric and electronic factors being constant, the constants in eq 1 depend on two processes, either one of which might be rate limiting[6] in a particular instance. The biological response (BR) will be determined by the amount of drug reaching the receptor sites in the test interval and the ability of the drug to bind hydrophobically with the receptor sites. We have postulated that the former process has a dependency on log P which can be approximated by the function: $dBR/dt \propto \exp[-(\log P - \log P_0)^2/a]$. We have further suggested that

$$\left(\frac{dBR}{dt}\right)_t = k_x k C \exp[-(\log P - \log P_0)^2/a] \quad (7)$$

In eq 7, C is the applied molar concentration of drug, k is the proportionality constant, and k_x is the rate or equilibrium constant for a single physical or chemical process governing BR which in the present case is governed only by the lipophilic interaction of drug and receptor. For a standard test, $(dBR/dt)_t$ can be replaced by a constant, and, since log P_0 is a constant for a given system, eq 7 can be converted to eq 8. We

$$\log \frac{1}{C} = -k_1(\log P)^2 + k_2 \log P + k_3 \log k_x + \text{constant} \quad (8)$$

have shown[40-42] that, *steric* and *electronic factors constant*, the binding of neutral organic compounds to purified proteins and enzymes in simple solution is a linear function of log P. Therefore we can replace the term $k_3 \log k_x$ in eq 8 with the term $k_4 \log P$ to obtain eq 9. As a working hypothesis, it seems reasonable to

$$\log \frac{1}{C} = -k_1(\log P)^2 + k_2 \log P + k_4 \log P + \text{constant} \quad (9)$$

assume that there is an ideal lipophilic character (log P_i) for the movement of organic compounds through mammalian tissue. This is different than the empirically found log P_0 in that we have separated out the

(39) A. Dorfman and L. R. Goldbaum, *J. Pharmacol. Exptl. Therap.*, **90**, 330 (1947).

(40) C. Hansch, K. Kiehs, and G. L. Lawrence, *J. Am. Chem. Soc.*, **87**, 5770 (1965).

(41) K. Kiehs, C. Hansch, and L. Moore, *Biochemistry*, **5**, 2602 (1966).

(42) C. Hansch, E. W. Deutsch, and R. N. Smith, *J. Am. Chem. Soc.*, **87**, 2738 (1965).

last partitioning step onto the receptors or into the very immediate region surrounding it. Taking the derivative of eq 9, we obtain

$$\log P_0 = \frac{\mathrm{d} \log \frac{1}{C}}{\mathrm{d} \log P} = -2k_1 \log P + k_2 + k_4 \quad (10)$$

Setting this equal to zero and solving, we obtain

$$\log P_0 = \frac{k_2}{2k_1} + \frac{k_4}{2k_1} \quad (11)$$

If our assumption that there is an ideal $\log P_i$ which is a constant for mammalian tissue holds, then we might write

$$\log P_0 = \log P_i + k_4/2k_1 \quad (12)$$

If $\log P_i$ is a constant and can be evaluated by the study of the diffusion of organic compounds through tissue, then we could make estimates of the energy of lipophilic interaction in the last partitioning step onto receptor or into the intimate receptor milieu. Of course, for many sets of drugs, the value for $\log P_0$ will be determined in part, at least, by metabolism (assuming equations similar to 4–6 hold in general). Actually, the value of about 1.9 found for $\log P_0$ for the bartiturates may turn out to be quite close to $\log P_i$. As mentioned above, this figure is close to $\log P_0$ (2.31) found for the penetration of benzeneboronic acids into mouse brain. The duration of these experiments was only 15 min, so that metabolic losses and elimination would be minimal. The work of Butler[43] offers some support for this view. He observed that for the oxybarbiturates the hypnotic effect paralleled the concentration in the brain. At the point of maximum concentration in the brain, the average concentration in the other tissues was only a little lower. Work with radioactive barbital[44] in mice indicated that whole body distribution tended to be uniform in 30 min at which time the brain seemed to contain a slightly lower concentration. About 1 hr was required for over-all uniform distribution. From another point of view we have noted, for instance, that $\log P_0$ for two different sets of plant growth regulators is also about 2.

As yet, we cannot be sure what effect the metabolism of barbiturates as implied by eq 4–6 has on the shape of eq 1. It may be that metabolism is a slow process relative to the BR measured, so that we can ignore its effect and still get good correlations, or that its effect is primarily through oxidation of C–H bonds and simply rate limited by $\log P$. If this is true (and it seems more likely), then one could consider this a kind of loss to lipophilic tissue. This effect would then be accounted for by the exponential term in eq 7 just as any other very strong binding of a nondestructive nature. Highly water-soluble compounds tend to be more rapidly excreted in the urine. This process may also be roughly rate limited by $\log P$. Hence the exponential term in eq 7 gives us a way of finding the ideal lipophilic character for a drug so that its chances of falling into a $\log P$ determined trap on the way to the sites of action will be minimal.

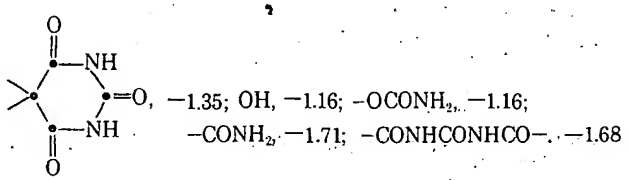
(43) T. C. Butler, *J. Pharmacol. Exptl. Therap.*, **100**, 219 (1950).
(44) H. Lal, C. F. Barlow, and L. J. Roth, *Arch. Intern. Pharmacodyn.*, **149**, 25 (1964).

The thiobarbiturates are extremely interesting when compared to all of the other sets of hypnotics examined in this report. Their unusually high $\log P_0$ value indicates that either they bring about their effect in a much more lipophilic region or on a more lipophilic set of receptors (the $k_4/2k_1$ term in eq 12 is higher). The possibility that more lipophilic centers in the brain are involved in the case of the thiobarbiturates can be inferred from the work of Goldstein and Aranow[45] and Roth and Barlow.[46] Their efforts have shown that the concentration of thiobarbiturates rises in the brain considerably above that in the blood plasma in a rather short time.

There appears to be an interesting relation between the more lipophilic character of the thiobarbiturates and their ability to uncouple phosphorylation.[36] Although the oxybarbiturates inhibit respiration, they do not appear to be as effective in uncoupling phosphorylation. The activity of phosphorylation uncouplers is closely associated with very high lipophilic character.[40,47,48] Our high $\log P_0$ for the thiobarbiturates is thus in line with other findings for a different mode of action for this class of hypnotics.

Certain less precise points can be made in connection with ideal lipophilic character for hypnotics. For example, a set of dialkoxymethanes,[49] $(RO)_2CH_2$, was tested for hypnotic activity. Although, because of the form in which activity was reported, we cannot treat these as was done above for the other hypnotics, the most active member of the series by simple inspection is the propyl derivative. Its $\log P$ is 1.85, based on the experimental value of 0.85 for the diethyl congener. It is interesting to note $\log P$ for some of the better known, potent CNS depressants: chloroform = 1.97, chloretone = 2.03, glutethimide = 1.90.

Certain guidelines for the design of the relatively nonspecific hypnotics such as those in Tables I and II seem evident from our analysis. The one common characteristic of the polar functional groups of the hypnotics of Tables I and II is that they are some of the most water solubilizing of the nonionic functional groups we have investigated.[11b] Their respective π values are



-1.35; OH, -1.16; $-OCONH_2$, -1.16; $-CONH_2$, -1.71; $-CONHCONHCO-$, -1.68

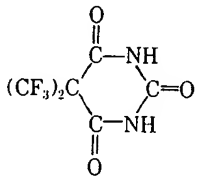
Another such function which has been used in hypnotics is the sulfone group. We do not have a π value for this function in an aliphatic system; however, π for CH_3SO_2 is -1.26 in the phenoxyacetic acid system. These highly water-soluble functions permit the largest possible apolar moiety to be incorporated into the drug without exceeding the $\log P_0$ of 2. In other words, the general over-all view is that the larger the lipophilic function the better, as long as we do not overstep $\log P_0$ of 2. One wonders what the meaning of this is mechanistically. Our feeling is that the barbiturates

(45) A. Goldstein and L. J. Aranow, *J. Pharmacol. Exptl. Therap.*, **128**, 1 (1960).
(46) L. J. Roth and C. F. Barlow, *Science*, **134**, 22 (1961).
(47) H. C. Hemker, *Biochim. Biophys. Acta*, **63**, 46 (1962).
(48) T. Fujita, *J. Med. Chem.*, **9**, 797 (1966).
(49) P. K. Knoefel, *J. Pharmacol. Exptl. Therap.*, **50**, 88 (1934).

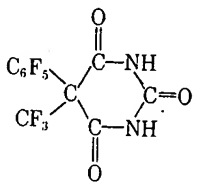
fall into the large class of nonspecific inhibitors of cellular-oxidative processes.[9] The more lipophilic these compounds are, the more potent they are as inhibitors of electron transport.[9] The larger the apolar function, the better they are able to distort a lipoprotein matrix and so disrupt electron transport. While this property is linearly related to log P over a rather great range of P values in isolated tissue or cells,[9] it is not in whole animals. This is in part due to the much more complex random walk from the site of introduction to the site of action and also to the restriction imposed by eq 4–6 which is more serious in whole animals.

To get more potent hypnotics, one might look at nonionic functions with larger negative π values. Probably little is to be gained here since these have been fairly well investigated.[31] Possibly the most is to be gained by designing molecules more resistant to metabolism. This could mean smaller doses and longer duration of action. We believe that the clue to getting around this difficulty with the hypnotics, or with other drugs, is to avoid having sp^3 C–H bonds next to groups which are capable of delocalizing a lone pair or lone electron. Evidence[37] strongly suggests that such bonds are rapidly and indiscriminately attacked in a very lipophilic section of the liver microsomes. This may be the reason barbiturates, substituted with only one alkyl group in the 5 position, are so weakly active.[50] This is probably the reason tertiary alcohols are so much more effective than primary or secondary. It is probably also the reason why compounds such as **157–162** with no α hydrogens turn out to be worthy of careful investigation. The barbiturate function itself seems very resistant to metabolic action, and it is well known that the diethyl derivative (log $P = 0.65$) is excreted more or less unchanged. It is only when log P gets in the range of 1.5 that serious destruction occurs. Unfortunately, the molecules with lower log P values are not only less potent, they are also more rapidly excreted in the urine.

A likely antidote for C–H bond oxidation would be to make perfluoro derivatives such as the following.



I



II

A π value for aliphatic CF_3 is not available, but it would not be far from the aromatic value[10] of 1.07. Compound I would have a log P close to diethylbarbituric acid, probably a little higher because of the inductive effect of the trifluoromethyl groups.[10] Compound II would be higher than phenobarbital because of the aromatic F atoms ($\Sigma\pi_F = 5 \times 0.15 = 0.75$). If the pentafluorophenyl function is stable to nucleophilic attack in the body, this should be a very potent CNS depressant of very long duration. Log P for compound I could be increased by adding CF_2 units. Such compounds might turn out to be tranquilizers of low dosage and long duration of action.

The knowledge that more or less hypnotic activity is to be expected with drugs having log $P_0 = 2$ could be helpful in minimizing such a side effect. For example, it is well known that antihistamines often have a depressant effect on the CNS. In some instances, the effect may be more specific than that of the hypnotics considered above. In fact, it may be related to that of congeners of morphine. When the effect is nonspecific, then one could minimize it by moving as far as practical from log $P = 2$ in the preparation of derivatives.

While the figure of log $P = 2$ is useful to have in mind when designing CNS drugs, particularly if one is dealing with neutral compounds, the considerations involved in the formulation of eq 9 and the results with the thiobarbiturates indicate that much higher log P values are essential for more specific activity. For example, chlorpromazine has a value of 5.35. It must be borne in mind that this figure is found for the neutral molecule, not the protonated form.[10] In fact, it may be the protonated form which aids in the movement through tissue of such an extremely lipophilic substance. The more nearly neutral CNS drug chlorodiazepoxide[51a] has log $P = 2.44$. Log P for diphenylhydantoin[51b] is 2.47.

For designing milder acting CNS depressants one could go to higher or lower log P values. Since toxicity often (but not always) appears to be linearly related to log P, compounds with lower log P values are interesting to explore. A case in point is meprobamate, log $P = 0.70$.

One should not assume that the results in this report or our previous ones establish the fact that a nice complete symmetrical parabola will always be found when log $(1/C)$ is plotted against log P with steric and electronic factors constant. In the majority of examples which we have considered, the investigation of increased lipophilicity was terminated with compounds slightly beyond the optimal log P_0. Although there are good examples[52,53] of complete parabolic curves, these are rare. More experimental work is necessary to establish the fact that higher order terms in eq 1 are not necessary.

The results in this paper support our view that log P_0 can be a helpful constant in drug design. Further work is in progress to establish the limits of its usefulness.

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(51) (a) Librium®; (b) Dilantin®.

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(53) E. W. Bousequet, P. L. Salzberg, and H. F. Dietz, *Ind. Eng. Chem.*, **27**, 1342 (1935).